IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

HERON THERAPEUTICS, INC.,	)	
	)	
Plaintiff,	)	
	)	
v.	)	C.A. No. 22-985 (WCB)
	)	
FRESENIUS KABI USA, LLC,	)	
	)	
Defendant.	)	

HERON'S RESPONSIVE POST-TRIAL BRIEF

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Table of Abbreviations

ABBREVIATION	MEANING	EXHIBIT NO.
'229 patent	U.S. Patent No. 9,561,229	JTX-1
'794 patent	U.S. Patent No. 9,974,794	JTX-7
AC	Doxorubicin/Cyclophosphamide	
Agarwal	Agarwal et al., Process Optimisation, Characterisation and Evaluation of Resveratrol-Phospholipid Complexes Using Box-Behnken Statistical Design, 3 INT'L CURRENT PHARMACEUTICAL J. 301 (2014)	JTX-67
ANDA	Abbreviated New Drug Application	
Asserted claims	Claims 9, 10, and 21 of the '229 patent and claims 9 and 10 of the '794 patent	
CINV	Chemotherapy-induced nausea and vomiting	
CN '845	Chinese Patent Appl. Pub. No. 102379845 (A)	JTX-71
Emend IV	Emend for Injection	
EP '279	Bombardelli et al., EP0441279A1 (published Aug. 14, 1991)	JTX-74
FBr.	Fresenius Opening Post-Trial Brief	
FDA	United States Food and Drug Administration	
Fell	Fell et al., *Intravenous Lipid Emulsions in Parenteral Nutrition*, 6 Advanced Nutrition 600 (2015),	JTX-76
Fresenius	Defendant Fresenius Kabi USA, LLC	
Fresenius's ANDA	ANDA No. 214639	
Fresenius's ANDA Product	The drug product that is the subject of ANDA No. 214639	
Hargreaves	Richard Hargreaves et al., *Development of Aprepitant, the First Neurokinin-1 Receptor Antagonist for the Prevention of Chemotherapy-Induced Nausea and Vomiting*, 1222 Annals N.Y. Acad. Scis. 40 (2012)	JTX-82
HBr.	Heron Opening Post-Trial Brief	
HEC	Highly emetogenic chemotherapy	
Heron	Plaintiff Heron Therapeutics, Inc.	
Hingorani	U.S. Patent Appl. Pub. No. 2013/0317016 A1	JTX-21
ISAE	Infusion site adverse events	
IV	Intravenous	
Jumaa	Jumaa et al., *Lipid Emulsions as a Novel System to Reduce the Hemolytic Activity of Lytic Agents*, Eur. J. Pharm. Sci. 2000 (285-290)	JTX-88
Kamat	Kamat and DeLuca, "Chapter 5: Formulation Development of Small and Large Volume Injections," in *Pharmaceutical Dosage Forms: Parenteral Medications, Third Edition*, 2010	JTX-92
Karavas	International Patent Appl. Pub. No. WO 2014/005606 A1	JTX-90

Table of Abbreviations (continued)

ABBREVIATION	MEANING	EXHIBIT NO.
Khan	Khan et al., *Basics of Pharmaceutical Emulsions: A Review*, 25 African J. Pharmacy & Pharmacology 2715 (2011)	JTX-91
Leal 2014	Leal et al., *Fosaprepitant-Induced Phlebitis: A Focus on Patients Receiving Doxorubicin/Cyclophosphamide Therapy*, 22 Support Care Cancer 1313 (2014)	JTX-137
Liu	Liu et al., *Progress in Research of Injectable Microemulsion*, 42 Chin. J. Pharm. 300 (2011) - Legaltranslation.biz	JTX-93
MEC	Moderately emetogenic chemotherapy	
NCCN	National Comprehensive Cancer Network	
NK-1	Neurokinin-1	
Patents-in-suit	U.S. Patent Nos. 9,561,229 and 9,974,794	
PFAT5	Population of large-diameter fat globules greater than 5 μm	
POSA	Person of ordinary skill in the art	
Rabinow	Rabinow, *Nanosuspensions in Drug Delivery*, SEPTEMBER 2004 | VOLUME 3, www.nature.com/reviews/drugdisc	JTX-183
RLD	Reference Listed Drug	
Strickley	Strickley, "Solubilizing Excipients in Oral and Injectable Formulations," *Pharmaceutical Research*, **2004,** *21*, 201-230	JTX-105
USP	United States Pharmacopeia	
Von Corswant	Von Corswant et al., U.S. Application No. 2001/0007663 (published July 12, 2001)	JTX-110
Wan	U.S. Patent Appl. Pub. No. 2011/0038925 A1	JTX-112
Washington	Washington, *Stability of Lipid Emulsions for Drug Delivery*, 20 Advanced Drug Delivery Revs. 131 (1996)	JTX-113
Yue	Yue et al., Process Optimization, Characterization and Evaluation In Vivo of Oxymatrine-Phospholipid Complex, 387 Int'l J. Pharmaceutics 139 (2010)	JTX-114
Zhou	Zhou et al., "Preparation of Aprepitant Emulsion for Intravenous Injection," *Chinese Journal of Pharmaceuticals*, **2012,** *43*, 1003-1006	JTX-115

I. INTRODUCTION

Fresenius failed to prove by clear and convincing evidence that the Asserted Claims would have been obvious over its thirteen-reference prior art combination. Fresenius's hindsight-driven argument is premised on the assertion that a POSA would have been motivated to "optimize" CN845's aprepitant emulsions for stability by drastically increasing emulsifier to arrive at the Asserted Claims. But its analysis is rife with legal and factual errors, and mischaracterizations of the testimony and the prior art.

There is no dispute that aprepitant's challenging physical properties, such as extremely low solubility (akin to "cement dust"), precluded its formulation as an IV drug product before Heron's Cinvanti®. Working backwards from Heron's success, Fresenius ignores not just the preceding decades of failure, but also that what scientists *actually did* when faced with that failure was to design more soluble drugs. Fresenius simply fails to justify why a POSA looking to design a safe and effective IV NK-1 receptor antagonist with minimal side effects would start with the aprepitant emulsions of CN845.

Fresenius's tortured arguments to the contrary are self-defeating. To overcome this history, and manufacture a motivation to optimize the purported stability of CN845, Fresenius asserts that "the new emulsion" of CN845 "solved" the problem of stable aprepitant emulsions for injection (FBr. 5, 14), all but ignoring the fact that CN845 contains no stability data. But if CN845's stability is the reason that a POSA would select it as a starting point, a POSA would not have been motivated to modify the very features of its formulation that lent it that stability. Fresenius nonetheless argues that the particular emulsifier content of CN845 had a profound effect on its stability and also that a POSA's optimization would drastically increase that emulsifier content *beyond* the (purportedly) already successful 10% upper limit of CN845 to match the claims. FBr. 14, 23, 27. Worse yet, this ignores Khan's clear statement, with which both parties' experts agree,

that "[a]t high emulsifier concentration emulsion instability occurs." JTX-91.5.

Fresenius mischaracterizes the record to argue that a POSA would be motivated by generic USP standards to test emulsifier content of up to 30% as part of the "routine" optimization of CN845. Not only does the USP lack any teachings about the direction to modify the prior art, but Fresenius's arguments also fly in the face of good science. Fresenius argues that CN845 revealed a completely novel hypothesis to ordinary artisans—that aprepitant is stabilized by forming a "complex" with egg lecithin, so increasing egg lecithin would increase stability. CN845 does not even mention complexation. Likewise, Fresenius relies on Washington, but ignores that the emulsions discussed in the portions of Washington it relies on used 1.2% lecithin. Perhaps worst of all, Fresenius gets its 30% optimization ceiling from Liu, a review of microemulsions—which the experts agree are ***not*** at issue in this case. Finally, Fresenius itself admits that "Zhou already gave an example of how do you do a routine optimization" of work including CN845 (FBr. 18), but never once mentions that Zhou found *decreasing* egg lecithin to 2.5% was optimal.

Undercutting Fresenius's entire premise, the only testing in this case shows that neither CN845 nor Zhou were physically stable in the first place. A POSA would treat them no differently than the industry's myriad other failed attempts. In the face of such prior art, Fresenius fails to prove that, at the priority date, a POSA would have reasonably expected an aprepitant emulsion with 14% egg lecithin to be physically stable, as its emulsifier content would have far exceeded that of any physically stable formulations that came before. Fresenius has not overcome any of the objective indicia of nonobviousness that Heron proved at trial, and its baseless written description argument ignores the specification's express disclosures that are co-extensive with the claims. Fresenius treats infringement as an afterthought—used to prop up invalidity rather than stand on its own. In the end, any one of the contradictions, scientific flaws, legal errors, or

mischaracterizations that Fresenius makes is enough to dispose of its defenses.

II. FRESENIUS FAILED TO PROVE THAT A POSA, WITHOUT HINDSIGHT, WOULD HAVE OBVIOUSLY ARRIVED AT THE INVENTION

A. Fresenius Failed to Prove that a POSA Was Motivated to Create a New Aprepitant Emulsion

In arguing that a POSA would have focused on an aprepitant emulsion, Fresenius asserts that "aprepitant was the *most* suitable option [for an IV formulation] at least because aprepitant was FDA-approved," and points to alleged "extra cost and more complex synthesis [of fosaprepitant] compared to aprepitant itself." FBr. 10-11 (emphasis in original).[1] But Fresenius ignores the significant downsides of trying to work with aprepitant that in fact resulted in no successful IV formulation of aprepitant until Heron's invention of Cinvanti®. HBr. 19. Merck created a new chemical entity, fosaprepitant, because aprepitant was such a difficult chemical (HBr. 53), other companies focused on fosaprepitant (including Fresenius) (HBr. 20), and Dr. Rabinow admitted a POSA working to develop an IV NK1 receptor antagonist would be looking to reformulate fosaprepitant (Emend® IV) (HBr. 19-20).

The trial also showed other NK-1 receptor antagonists available to a POSA. HBr. 18-20. Dr. Rabinow dismissed these by asserting that "most of them were in phase one or phase two." TD1 279:15-21 (Rabinow). That was wrong. Rolapitant and netupitant had, as Dr. Hale explained, completed Phase III clinical studies and were "successes," making them viable starting points for a POSA facing the problem to be solved.[2] TD3 944:17-945:11; 951:23-952:10 (Hale).

Fresenius's argument that this evidence was irrelevant because a "'lead compound'-type

[1] Unless stated otherwise, all internal quotations and citations are omitted, and all emphases added.

[2] Fresenius asserts that rolapitant and netupitant "were already formulated as injectables, without the use or need for prodrugs, and without any published concerns or stated objectives for improvement," (FBr. 5 (citing Dr. Hale's testimony)), but Dr. Hale did not discuss the formulations of these drugs. And, in fact, netupitant was initially approved as an oral drug only. *See* PTX-5.

analysis only applies in cases involving modifications to chemical compounds and is legally irrelevant in formulation cases" is misplaced. FBr. 12-13 (citing *Bayer Pharma AG v. Watson Labs, Inc.*, 874 F.3d 1316, 1328-29 (Fed. Cir. 2017)). This is neither a lead-compound case nor a case like *Bayer.* In *Bayer,* the issue was whether a motivation existed to develop a particular active ingredient as an oral disintegrating tablet (ODT) in view of prior art references disclosing ODT formulations of the same class of drugs. *Bayer*, 874 F.3d at 1324. Here, the issue is the motivation of a POSA to work with an exceedingly difficult chemical entity in designing a new IV NK-1 receptor antagonist. TD4 1272:14-22 (Little). Heron is not, as Fresenius says, "argu[ing] that the obviousness analysis requires ruling out all NK-1 receptor antagonists before considering aprepitant." FBr. 12.

Heron's position is that Dr. Rabinow exercised hindsight in giving the POSA, who lacks infinite resources, a myopic focus on aprepitant emulsions. The Federal Circuit recognized in *Insite Vision Inc. v. Sandoz, Inc.* that "an overly narrow statement of the problem to be solved can represent a form of prohibited reliance on hindsight." 783 F.3d 853, 859 (Fed. Cir. 2015); *see* HBr. 18. Fresenius tries to dismiss *Insite* by incorrectly asserting that it was "not directed to 'specific formulations'" (FBr. 12), but when addressing the *formulation claims* at issue, the court recognized that a POSA "would not have been motivated to use the water-based polymeric solutions of the prior art in an azithromycin formulation because azithromycin was considered insoluble and unstable in water." *Id.* at 862.

Fresenius also ignores all formulation choices confronting a POSA when it argues a POSA had an "interest in intravenous aprepitant, ***including*** emulsions." FBr. 11. The evidence, including Strickley and Kamat, showed intravenous formulation techniques that a POSA would have considered that were not emulsions, and observed that intravenous emulsions were rarely used for

a commercial product. HBr. 20-21. Indeed, Dr. Rabinow recognized that nanosuspensions were a viable formulation approach. HBr. 21.

Fresenius asserts that "CN845 expressly confirmed problems with existing approaches that the new emulsion solved," and that a "POSA would have recognized why emulsions solve the aprepitant formulation solubility problem." FBr. 5-6. But CN845 said nothing about other formulation approaches and CN845 lacked any data regarding any testing of the purported aprepitant emulsions.[3] TD1 318:9-11 (Rabinow); *see also id*. at 189:7-14, 359:18-360:11 (Rabinow); TD4 1245:20-23 (Little). And by pointing to this one reference Fresenius assumes away all the other options confronting a POSA who does not have the benefit of hindsight. Also, Fresenius's argument proves too much; if its assertion were true, which it is not, then the POSA would have lacked a motivation to change the formulations described in CN845.

B. Fresenius Failed to Prove a POSA, Without Hindsight, Would Have Applied Routine Experimentation to Arrive at the Invention

1. Fresenius Begins with an Assumption It Did Not Prove—That a POSA Would Have Optimized CN845 in a Way Other Than Zhou

Fresenius asserts that "a POSA looking to make an intravenous formulation of aprepitant would have been motivated to take CN845's teaching [including 0.5-10% emulsifier] and optimize emulsion formulations according to USP 1 and USP 729." FBr. 13-14; FBr. 6, 17, 18. This is a card trick. The USP is just a compendium of quality control standards for the pharmaceutical industry. It provides a POSA with "no guidance whatsoever" on how to meet its criteria, let alone to go in any particular direction from CN845. TD4 1267:1-1268:15 (Little) ("[I]t's difficult for me to understand how you would say that the presence of all these USP standards makes somebody

[3] Fresenius's assertion that "CN845 transformed the state of the art in 2012" (FBr. 14), cannot be reconciled with the fact that none of the experts were aware of CN845 before this litigation (HBr. 26-27) and there is no evidence that CN845 provided stable emulsions (HBr. 9-10).

optimize, especially in a given direction for any drug product."). Fresenius cannot use the USP to sidestep Zhou and ignore that Zhou purported to optimize its author's prior work, which included CN845, and arrived at just 2.5% egg lecithin. HBr. 25-27; FBr. 34-36.

Also, as explained in Heron's opening brief, Fresenius picks and chooses from CN845's ranges and genuses selecting among both its preferred and non-preferred ingredients and amounts. FBr. 7-8, 24-25, 27-31; HBr. 24, 29-30, 41-43. Fresenius does this without an explanation. In doing so, Fresenius also ignores the low emulsifier percentages existing in the prior art emulsions, consistent with Zhou. HBr. 31.

Moreover, any motivation to modify CN845 (or Zhou) is undermined by Fresenius's repeated assertion that CN845 and Zhou had already "solved" the problem of a stable aprepitant emulsion. *E.g.*, FBr. 5, 7, 10, 12 ("[T]here was no difference in what the Patents-in-Suit set out to do and what the prior art already did."), 13. If the POSA, according to Fresenius, believed CN845 solved the difficulty of working with aprepitant, then a POSA would avoid departure from CN845. Moreover, Examples 4 and 5 of the patents-in-suit, the ***only*** testing evidence of record for either CN845 or Zhou, showed that neither one was stable.[4] HBr. 9-10; *see also* HBr. 38. Hindsight can be the only explanation for Fresenius's convoluted and legally erroneous defense.

a. Fresenius's Proposed "Optimization" Improperly Isolates the Claim Limitations from the Invention as a Whole

Instead of analyzing whether "the claimed invention as a whole would have been obvious," 35 U.S.C. § 103, Fresenius has the POSA addressing the limitations one-by-one, and searching

[4] Fresenius cannot point to CN845's lack of data, and Zhou's lack of PFAT5 or crystal data, as a motivation to disregard CN845 and Zhou. *See, e.g.*, FBr. 8, 21, 34-36. That is just hindsight. Even if a POSA had tested Zhou and seen that it rapidly crystallized, as was done in Example 5 of the patents-in-suit, there is no reason why a POSA would not have simply done what Merck actually did—refocus on other NK-1 antagonists or formulation approaches.

within CN845's broad lists of ingredient choices and percentages (and even beyond CN845 for emulsifier amount and sodium oleate). FBr. 24-31 (admitting that "the claim limitations are addressed separately"). Fresenius failed to consider how varying these ingredients and their percentages without hindsight would impact the overall formulation. HBr. 41-42 (citing *ModernaTx, Inc. v. Arbutus Biopharma Corp.*, 18 F.4th 1364, 1376 (Fed. Cir. 2021)).

Fresenius asserts that Heron has not shown "criticality" (FBr. 24-31), but the record provides no legal basis for Fresenius to shift the burden to Heron or require criticality. Fresenius relies on *In re Peterson*, 315 F.3d 1325, 1329-30 (Fed. Cir. 2003), but it does not apply here. *See, e.g.*, FBr. 16-17, 23-24. Fresenius failed to show that the overlapping range is actually taught by the prior art. Here, the claimed 14% egg lecithin ***does not overlap*** with ranges of emulsifier permitted in CN845—which Dr. Rabinow agreed disclosed only up to 10%. HBr. 46; TD1 330:21-331:13 (Rabinow). Likewise, CN845 does not disclose the use of sodium oleate.[5] HBr. 46. And, as in *Genetics Inst.*, *LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291 (Fed. Cir. 2011), the disclosures of ingredient and percentage choices within each category of ingredients (*e.g.*, emulsifiers) in CN845 is "so broad as to encompass a very large number of possible distinct compositions thus requiring nonobvious inventions," such that "*Peterson* does not extend to the facts of this case." *See* HBr. 46-47 (quoting *Genetics*, 655 F.3d at 1306-07).

Fresenius also failed to show that its proposed "optimization" would have been routine (or had a reasonable expectation of success) in the face of the unpredictable interactivity of the components of aprepitant emulsions and the lack of success in the art. HBr. 9-10, 44-45. As in *ModernaTx*, "[t]he unpredictable interactivity between the various . . . components renders the

[5] Fresenius is also wrong that Examples 7 and 8 of CN845 "bracketed all of the claim limitations . . . with the exception of 14% lecithin." FBr. 23; HBr. 24, 29-30 & n.17. Nor did they use the same emulsifier, oil, protective agent, or co-emulsifier as each other. PDX4-4; JTX-71.17.

claims . . . nonobvious." 18 F.4th at 1373-77; HBr. 41-42. *ModernaTx* recognized that "evidence that the variables interacted in an unpredictable or unexpected way could render the combination nonobvious" (18 F.4th at 1376), and the evidence in this case shows that aprepitant emulsions are just such a system:

> "[S]tability in the formulation is a result of several things together. . . . [Y]ou can't just say, for instance, that stability is driven by emulsion concentration. So what you're going to do is you're just going to increase the emulsi[fier] (*sic*) concentration to get that stability. . . . [T]hat's not an accurate view of how emulsion stability works and emulsifiers work. But you would be looking at that whole thing and what all the components are in terms of how that contributes to stability."

TD4 1316:17-1318:22, 1286:14-1288:13, 1426:1-13 (Little); *see also, e.g.*, TD4 1294:19-1295:24, 1299:15-1300:16, 1278:6-1279:1, 1309:9-1310:23, 1321:14-20, 1416:18-1417:16 (Little); TD2 474:1-14, 506:13-20, 508:1-16 (Han); TD2 547:23-548:2, 549:19-550:4 (Ottoboni). Merely "provid[ing] evidence of general considerations to be taken into account with respect to each individual component" is insufficient where there is a "fail[ure] to address the interdependence of the claimed components and how adjustments would affect the [composition] as a whole." *See ModernaTx*, 18 F.4th at 1376; HBr. 41-42. The additional cases Fresenius relies on are inapposite. The claims at issue in *Pfizer, Inc. v. Apotex, Inc.* and *Merck & Co. v. Biocraft Lab'ys, Inc.* were directed to a species belonging to a prior art genus. 480 F.3d 1348, 1361 (Fed. Cir. 2007); 874 F.2d 804, 806 (Fed. Cir. 1989). And the claims at issue in *Merck Sharp & Dohme Corp. v. Hospira, Inc.* were directed to a process for preparing a known compound, where the process steps were either literally disclosed in the prior art or conventional. 874 F.3d 724, 731 (Fed. Cir. 2017).

At bottom, a POSA seeking to optimize CN845 would not have simply ignored that the same researchers had already gone on to report an optimized system in Zhou. HBr. 29-30. Even Fresenius and Dr. Rabinow admit that "Zhou already gave 'an example' of 'how you do a routine optimization.'" FBr. 18 (quoting TD1 224:8-20 (Rabinow)). Moreover, if a POSA is choosing

CN845 or Zhou because they provide stable aprepitant emulsions, why would a POSA have been motivated to not only abandon the emulsifier amounts optimized in Zhou but even depart from the broad ranges of CN845? The POSA would not. *See Eisai Co. Ltd. v. Dr. Reddy's Lab'ys. Ltd.*, 533 F.3d 1353, 1358 (Fed. Cir. 2008) ("The record, however, shows no discernible reason for a skilled artisan to begin with lansoprazole only to drop the very feature, the fluorinated substituent, that gave this advantageous property.").

2. Fresenius Failed to Prove That a POSA Would Have Been Motivated to Use 14% Egg Lecithin with the Remaining Claim Limitations

To carry out the hindsight task of asserting a POSA would have made an aprepitant emulsion using more than 10% emulsifier, Fresenius crafts a daisy chain of false rationales and mischaracterizations of prior art that a POSA would not combine as a matter of science.

a. CN845 and Zhou Did Not Disclose Complexation

Fresenius asserts that "CN845 and Zhou involved forming complexes" between aprepitant and egg lecithin. FBr. 15. But, neither CN845 nor Zhou even mention complexation. HBr. 34; TD1 181:20-23, 354:16-19 (Rabinow). In order to read complexation into CN845 and Zhou, Fresenius makes three fundamentally flawed arguments, each of which failed to establish that a POSA would have been motivated to increase the emulsifier amount beyond CN845's 10% limit.

First, Fresenius asserts that Bombardelli (*i.e.*, EP '279), Yue, and Agrawal showed "phospholipid drug complexes [were] known to a POSA". FBr. 15. Fresenius simply ignores that none of the drug molecules in these documents were chemically similar to aprepitant or even in intravenous formulations. HBr. 35. Moreover, each of those documents "talk about a ratio of lecithin to the active ingredient of ***3:1 or less***." TD1 356:10-14 (Rabinow); *see also* TD4 1306:13-20 (Little). In contrast, the Asserted Claims use 14% egg lecithin in a ratio of egg lecithin to aprepitant of ***20:1***. TD1 330:10-13 (Rabinow).

Second, Fresenius asserts that the manufacturing process in CN845 purportedly "offered complexation opportunity." FBr. 15-16. But Dr. Rabinow's conclusory testimony on manufacturing (*e.g.*, TD1 154:4-155:15 (Rabinow)) does not establish that "a POSA would have concluded" (FBr. 15) that aprepitant-egg lecithin complexes formed and enabled the CN845 emulsions. *See* HBr. 34. As Dr. Little explained, "just saying that you can put these in ethanol doesn't mean you're trying to make a complex." TD4 1386:2-1386:22 (Little). Moreover, Dr. Rabinow admitted that Example 6—which contained 0.5% lecithin and was one of the "preferred embodiments" of the "present invention" in CN845—did not sufficiently complex despite being manufactured by this process. HBr. 34-35; TD1 350:7-352:15 (Rabinow). Notably, Fresenius does not point to the manufacturing process in Zhou, as it does not use this step. *See* JTX-115.6.

Third, Fresenius baldly asserts that because CN845 used "substantially more emulsifier" than "standard emulsions" (1.2%), a POSA would have drawn the conclusion that a complex was formed between aprepitant and the emulsifier. *See* FBr. 15, 27. But, Dr. Rabinow admitted that CN845's preferred examples include formulations (*e.g.*, Example 6) that use *less* than 1.2% egg lecithin—and, conveniently, do not sufficiently complex. *See* TD1 350:7-352:15 (Rabinow). He offers no actual evidence for this conclusory line drawing. Nor can it be reconciled with his opinions that only complexed prior art aprepitant emulsions were stable. HBr. 34 (citing TD1 366:5-11 (Rabinow)). Dr. Rabinow also admitted that other CN845 examples did not use a phospholipid emulsifier at all (*e.g.*, Examples 2, 3, and 8), and thus could not have complexed with aprepitant, even under his unsubstantiated hypothesis. HBr. 34-35.

Fresenius asserts that "more emulsifier means more opportunity for the drug to complex" (FBr. 15-16), but, as Dr. Little explained, that does not make scientific sense. *E.g.*, HBr. 37 n.20; TD4 1228:9-1231:12, 1386:2-1386:22 (Little). Moreover, Zhou took the author's previous work

into account—including the 10% emulsifier disclosed in CN845—when optimizing emulsifier to just 2.5%. *See* HBr. 35; JTX-115.1, 7, 9. Even if a POSA were to view CN845 as teaching aprepitant-egg lecithin complexes, it would necessarily be limited to, at most, CN845's disclosed range of 0.5-10% egg lecithin. And, at that point there would have been no motivation to further increase emulsifier to provide "more opportunity for the drug to complex with the emulsifier" as Fresenius asserts. *See* FBr. 15-16.

b. Fresenius Failed to Establish that Washington Taught Increasing Emulsifier Beyond the 1.2% Discussed Therein

Fresenius mischaracterizes Washington as teaching a POSA that "increasing emulsifier levels would both make oil globule sizes smaller and increase interface surface area, ***providing more places for more drug to remain stable over time***." FBr. 9; HBr. 36; JTX-113.9.[6] Fresenius relies on Dr. Rabinow's discussion of Washington's disclosure that "it is often necessary to post-load emulsions with [Class III drugs], in order to have a large surface area available for loading." *See* FBr. 9 (citing TD1 175:24-176:14 (Rabinow)); JTX-113.9. But, Washington merely provides a method of how to manufacture a Class III drug emulsion (post-loading as opposed to pre-loading the active ingredient) and says nothing about the amount of emulsifier to use or its effect on surface area. *See* JTX-113.9; FBr. 26 (quoting TD1 176:15-177:2 (admitting that his assertion was at most "an implication" from Washington) (Rabinow)). And, the only emulsions described in Washington that discuss loading a drug at the interface used the conventional 1.2% lecithin, with no suggestion of any shortage of surface area. HBr. 36 (citing TD1 364:8-365:21; JTX-113.2).

Further illustrating Fresenius's hindsight interpretation of Washington, both CN845 and

[6] To the extent Fresenius now argues that CN845 independently taught increasing emulsifier to increase surface area (*see, e.g.*, FBr. 16), it is wrong. Fresenius cites no discussion in CN845 about the effect of increasing emulsifier—let alone on surface area, droplet size, or drug loading on the interface—because there is no such discussion.

Zhou pre-load aprepitant before the emulsion is formed—as opposed to post-loading, like in Washington. JTX-71.14; JTX-115.6. And, as Dr. Little explained, too much emulsifier could lead to instability and actually *decrease* interface surface area. TD4 1426:1-13 (Little).

c. Khan Did Not Teach Increasing Emulsifier for Stability

Fresenius next overextends Kahn by asserting it "would have motivated a POSA to use more emulsifier." FBr. 26 (purporting to quote JTX-91.5).[7] What Khan actually says is more limited: "The amount of emulsifying agent is one of the most important factors having an influence on the emulsion stability." JTX-91.5; *see also* 169:1-13 (Rabinow). Khan also recognized that "[a]t high emulsifier concentration emulsion instability occurs because of rapid coalescence," citing a study showing that even 0.5% emulsifier can destabilize some emulsions. JTX-91.5; JTX-79.4; HBr. 36-37 & n.20; *see also* TD4 1286:14-1288:13 (Little). Indeed, Dr. Rabinow admitted that "there is a point . . . at which the amount of emulsifier clearly becomes counterproductive."[8] TD1 169:1-13, 249:18-251:14, 331:23-336:17 (Rabinow). In addition, nothing in Khan would motivate a POSA to ignore the general principle in formulation sciences that "when you add something, you want to add it to the smallest amount that you can." TD4 1286:14-1288:13 (Little); HBr. 37-38. Nor does Khan tell a POSA to ignore the totality of the prior art—including CN845's 10% limit for emulsifier, Zhou's optimized 2.5% emulsifier, and other post-CN845 references' continued use of the industry-standard, low-single-digit emulsifier levels (*e.g.*, Hingorani at ~1%)—and instead test as much as 14%. HBr. 25-26, 37-38; TD4 1282:20-1283:24 (Little).

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[7] Fresenius adds Khan to its obviousness combination mid-brief (FBr. 27), despite initially omitting it (FBr. 13-14). This malleability reflects the amorphous and convoluted nature of Fresenius's thirteen-reference obviousness combination, and only serves to further demonstrate the nonobviousness of the Asserted Claims. HBr. 22.

[8] Dr. Rabinow's "take-home lesson" from Khan was that "people are instructed to determine the optimal concentration window," such that "you identified what is too low a level and what is too high a level." *See id.*; HBr. 37.

d. A POSA Would Not Have Looked to Unrelated Art Like Liu

Fresenius repeatedly mischaracterizes Liu as discussing emulsions. *See* FBr. 19 ("Liu showed that 5-30% surfactant . . . was already used for making emulsions."); FBr. 1 ("the prior art showed up to 30% emulsifier had already been used"). Liu, however, deals with microemulsions, which, the parties' experts and even Fresenius all agree, are distinct from the aprepitant emulsions at issue in this case. HBr. 32; TD1 161:3-162:24, 190:15-191:8, 313:25-314:5 (Rabinow), TD4 1240:19-1241:16, 1289:13-1290:24, 1291:21-25, 1298:19-1299:5 (Little); FBr. 19 ("[A] POSA would understand that CN845 technically made emulsions."). Microemulsions are thermodynamically stable whereas emulsions are not, which implicates entirely different stability-related design constraints between the two systems. HBr. 32. The Court has recognized that this thermodynamic instability—which is absent from microemulsions—is what, *e.g.*, causes emulsions to undergo coalescence over time, increasing particle size. *See* D.I. 54 at 3. Microemulsions also use different components than emulsions, including different oils, emulsifiers, emulsifier blends, and amounts of each, and Fresenius identifies no microemulsions that actually use egg lecithin. HBr. 32-33.

Contrary to what a POSA would do, Fresenius focuses on the generic statement that "the amounts of surfactants used in microemulsions (5~30%) are relatively large," and not these significant differences between the two formulation systems. TD4 1289:13-1290:24, 1294:19-1295:9, 1300:22-1301:5, 1301:20-1302:12 (Little). Fresenius attempts to twist Dr. Little's testimony to imply that he said there is a "substantial[] overlap" between emulsions and microemulsions. FBr. 19. Dr. Little merely explained that sometimes scientists make a "mistake" and refer to "micron-sized emulsions" as "microemulsions" even though that term had historically been used in the art to describe "emulsions that are thermodynamically stable." *See* TD4 1422:20-1424:2 (Little). Dr. Rabinow agrees. *See* TD1 161:3-162:24 (Rabinow). Moreover, Von

Corswant expressly describes microemulsions as "contrary" to emulsions when differentiating the two systems (including via thermodynamic stability), consistent with Dr. Rabinow's testimony on cross-examination. JTX-110.3 (¶ 9); TD1 341:1-23 (Rabinow). To be clear, it is undisputed that formulations in CN845 and Zhou are not microemulsions. HBr. 32. Fresenius cannot point to a single reference teaching that the knowledge of one applies to the other. HBr. 32. Nor has Fresenius identified a single prior art formulation that falls between microemulsions and emulsions. FBr. 19; HBr. 32 n.19.

In an implicit recognition of these flaws, Fresenius's brief opts for misdirection—saying "Liu taught the safety of using high amounts of 'phospholipids.'" FBr. 16, 19. Liu does not identify any microemulsion that contains 30% emulsifier, let alone one that was shown to be safe and effective. Regardless, even if this were true, it would have no bearing on whether Liu would motivate a POSA to increase emulsifier to achieve a stable aprepitant emulsion. As Dr. Rabinow admitted, "thermodynamic stability has nothing to do with the safety of phospholipids." HBr. 33; TD1 341:24-342:11 (Rabinow). Moreover, Fresenius ignores that, even though Zhou post-dated Liu, its authors did not apply Liu's microemulsion teaching by testing up to 30% egg lecithin. *E.g.*, FBr. 27, 30, 36. Indeed, Khan would have suggested that they should not. *Supra* § II.B.2.c.

e. Fresenius's Improper Attempt to Ignore the Teaching of Zhou

Fresenius carefully avoids the true teachings of Zhou, as doing so would discredit Fresenius's obviousness arguments. For example, Fresenius calls Zhou a "proof of concept" of a stability-optimized aprepitant emulsion. *E.g.*, FBr. 5, 8, 14. But, despite Fresenius's great emphasis on the importance of emulsifier content to stability, it never once mentions that Zhou's optimization found that 2.5% egg lecithin was best. Fresenius says that CN845 and Zhou "both published" in 2012 (FBr. 5), but never mentions that CN845 was filed in November 2011, or that Zhou was submitted by the same author in 2012, making it optimization follow-on work that would

have informed any POSA's view of CN845. TD4 1253:2-9 (Little); JTX-71.8, JTX-115.1.

Fresenius likewise says Zhou "picked a fixed aprepitant and oil concentrations" (FBr. 8), but omits that a POSA would have recognized that even these fixed amounts were *part* of the author's larger optimization, determined based on the previous work. TD4 1253:2-9, 1254:4-24 (Little); JTX-115.7 ("Through pre-experimental and single factor analysis, it was primarily determined that the emulsion recipe was: 0.25% of APT, 15% of soybean oil, 2~4% of egg yolk phospholipid (A), 0~0.2% of oleic acid (B), 0~0.5% of polaxamer (C) and 0~3% of glycerol (D)"). A POSA reading Zhou would have understood that the selection of these amounts and ranges "to continue investigating the impacts of the factors" via an "[o]rthogonal design method" was not arbitrary. *Id*. A POSA would have had no motivation to undo the Zhou group's optimization work—which zeroed in on 2.5% from 4%, and 10% before that—and instead reverse the trend taught by the totality of the prior art to suddenly increase emulsifier to 30%, or even 14%. TD4 1397:24-1398:7 (Little) ("[Y]ou've got to answer a question for me that nobody has been able to answer. Why are we modifying from a formulation that somebody has optimized to be at the stability?").

f. Although Not Necessary, the Evidence Shows "Criticality"

Fresenius incorrectly asserts that "the trial evidence showed no proof of criticality that the claimed 14% was special" because "Dr. Little admitted that Example 3 in the Patents-in-Suit used the lower 11.7% lecithin and still satisfied the Court's claim construction for a 'physically stable' formulation." FBr. 23-24. As explained above, this is not a *Peterson* case, and Heron has no burden to prove criticality. *See supra* § II.B.1.a; HBr. § IV.G. Even so, the patents-in-suit's example with 11.7% lecithin has no place in a criticality analysis. Criticality is demonstrated "by showing that ***the claimed range*** achieves unexpected results ***relative to the prior art range***." *Peterson*, 315 F.3d at 1330. Here, the "claimed range" is 14% lecithin, and the "prior art range"

has a ceiling of 10% emulsifier, with most examples, including Zhou's optimal one, having much less. Moreover, Heron established that the difference in physical stability between the claimed invention and the prior art, the correct comparison, was one of kind, not degree. HBr. § IV.G.

3. Fresenius Failed to Prove That a POSA Would Have Been Motivated to Use Sodium Oleate as a pH Modifier

CN845 and Zhou did not disclose the use of sodium oleate. Despite this, Fresenius asserts that "a POSA would have understood that sodium oleate was an obvious and suitable choice" as a pH modifier. FBr. 27. Each of Fresenius's convoluted arguments fails.

First, Fresenius incorrectly asserts that because "a POSA understood that oleic acid was already a constituent part of egg yolk phospholipid" a POSA would have selected sodium oleate. FBr. 27. Fresenius offers no evidence egg lecithin actually degrades to release oleate in the way it suggests. HBr. 39-40. Fresenius also provides no explanation for why a POSA would ignore more common pH modifiers (*e.g.*, the strong base sodium hydroxide) in favor of a weak base degradant—something that is not wanted in the system. HBr. 39. *Second*, Fresenius asserts that "even if a POSA did not separately add sodium oleate, a formulation containing any sodium-based pH adjuster would" create sodium oleate because oleic acid is a degradants of egg yolk lecithin. FBr. 28. Fresenius appears to be arguing that sodium oleate is inherently present in the prior art, but the standard for inherency is a high one that Fresenius does not even attempt to meet. *See Endo Pharm. Solutions v. Custopharm Inc.*, 894 F.3d 1374, 1381-82 (Fed. Cir. 2018) (inherency "may not be established by probabilities or possibilities," it is a "rigorous standard" and must be necessarily present). Further, if sodium oleate were inherently present in any formulation with egg yolk lecithin, it would improperly render superfluous the sodium oleate claim limitation. Regardless, Fresenius has not proven that sodium oleate or sodium would be present in any appreciable amount. HBr. 39-40. *Third*, Fresenius asserts that given Zhou's disclosure "[r]ather

than adding oleic acid and then adding sodium hydroxide to get a basic pH, a POSA would have known to use sodium oleate instead." FBr. 28. It defies logic that a POSA would have interpreted the benefits of adding an acid as a motivation to add a base. *See* TD4 1249:11-19 (Little). Even if some of the alleged benefits were due to properties of oleic acid other than pH adjustment, the Zhou formulation, which Fresenius describes as stable, does not have a separate pH adjusting step.

Fresenius is also wrong "that prior art review articles called [sodium oleate] out as commonly used with emulsions." FBr. 28. Fresenius points to Fell, which is not prior art. HBr. 41. Fresenius also points to Wan and Jumaa, but these references show that sodium oleate presents a risk of hemolysis, so a POSA would not have been motivated to use it. *See* HBr. 40-41. Fresenius incorrectly asserts that Jumaa—which referred to sodium oleate as a hemolytic agent—"clarified that any hemolysis associated with sodium oleate was not an issue in the emulsion setting." FBr. 28 (citing Tr. 383:10-385:2 (Rabinow) (adding phospholipids into the emulsion "drastically reduce[s] the hemolysis")). But, there is no dispute that even with the specific soy lecithin formulations tested in Jumaa sodium oleate did cause hemolysis at 0.3%. JTX-88.2-3 (Figure 1). Moreover, the emulsions in Wan actually used egg lecithin, unlike Jumaa, and still found sodium oleate was hemolytic. JTX-112.38; HBr. 40. Even if the hemolysis risk varies with the formulation, it still raises the question of why a POSA would have used sodium oleate to modify pH over conventional and safe pH modifiers like sodium hydroxide.

Grasping at straws, Fresenius tries to use Heron's own work or misconstrue the prosecution of the patents-in-suit, none of which can satisfy Fresenius's burden. Fresenius asserts that "[e]specially given the fact that the Asserted Claims require no particular amount of sodium oleate, a POSA would have considered it an obvious choice" (FBr. 29), but a POSA would not have known of the claims or been influenced by them. Fresenius also asserts that Dr. Little "apparently

had not reviewed Heron's own work that showed sodium hydroxide 'instead of sodium oleate' worked just as well to create stable formulations" (FBr. 29)—but a POSA likewise would not have known of Heron's internal work. Fresenius also incorrectly asserts that "during prosecution, Heron recognized that sodium oleate was just another excipient," and argues that "Heron did not respond [to a Patent Office rejection by] saying that sodium oleate was new or unique." FBr. 28. But Heron responded by stating that "[u]se of sodium oleate to adjust pH of the emulsions would not have been obvious" (JTX-2.110), and specifically that Zhou did not disclose its use (JTX-2.119).

4. Fresenius Failed to Prove That a POSA Would Have Been Motivated to Combine the Other Claimed Ingredients in the Claimed Amounts

As explained above, Fresenius's obviousness analysis fails for focusing on formulation ingredients and concentrations individually, rather than the invention as a whole. *See supra* § II.B.1.a. Fresenius improperly cherry-picks soybean oil, sucrose, ethanol, and the amounts of each (and of aprepitant itself) from CN845 by working backwards from the claims. *See* HBr. § IV.E.3. Moreover, the burden is not on Heron to establish the "criticality for the claimed" concentration of aprepitant (FBr. 24), soybean oil (FBr. 25), sucrose (FBr. 30), and ethanol (FBr. 31), or why a POSA would not have arrived at the claimed invention. *See supra* § II.B.1.a.

C. A POSA Would Not Have Had a Reasonable Expectation of Success

Fresenius starts with a factually flawed, circular argument: a POSA would have reasonably expected to make a stable aprepitant emulsion when modifying CN845 because "CN845 and Zhou demonstrated to a POSA that aprepitant emulsions were physically stable." FBr. 33; HBr. 9-10. The stability data of record for CN845 and Zhou—Examples 4 and 5 of the patents-in-suit with as much as 9.95% egg lecithin—show neither was physically stable. HBr. 9-10, 45.

Fresenius points to the particle size range and autoclaving step of CN845 as proof of stability (FBr. 20, 33), but CN845 reports no actual particle size data for any of its emulsions and

autoclaving is a way to quickly sterilize a sample, not a stability test. HBr. 45; TD4 1226:15-1227:20 (Little).[9] Similarly, Zhou's optimization for a different stability parameter (K_e), compliance with USP particle-size standards, or *absence* of PFAT5 and crystal data (FBr. 20-21, 33-35) would not have told a POSA that using ***over five times*** as much emulsifier (14%) would result in a stable emulsion. *See* TD4 1321:21-1322:6, 1325:4-1326:1 (Little). In the testimony Fresenius cites for support, Dr. Rabinow simply does not opine that "because" Zhou optimized for K_e, a POSA would know that further optimization would be required to meet USP. *See* FBr. 34 (citing TD1 213:20-214:17). Even so, the absence of PFAT5 data in CN845 and Zhou is not a logical basis to assert that a POSA would think the USP PFAT5 criterion had been met, let alone to reasonably expect that it would be after modifying that prior art to meet the Asserted Claims. *See* FBr. 34; TD1 330:17-20 (Rabinow). Nor could a POSA "take as a promising sign" that Zhou did not report seeing any crystals (FBr. 35), when Zhou did not actually report any crystal results at all (TD1 325:18-326:1 (Rabinow)). *See also* HBr. 9-10 (showing crystals *do* form for Zhou).

Fundamentally, neither CN845's disclosure (0.5-10%), Zhou's reduction (2.5%), nor any of Dr. Rabinow's other emulsion prior art used anywhere near the claimed 14% egg lecithin. If anything, a POSA would have thought that using dramatically more than the industry-standard ~1% emulsifier of the only FDA-approved emulsions would not have resulted in a stable formulation, particularly in view of, *e.g.*, Khan, which warns *against* using too much emulsifier. *See* HBr. 31, 44-45; *supra* § II.B.2.c. Fresenius is simply incorrect that the "prior art disclosed no upper boundary beyond which emulsifiers would not help aprepitant emulsions." FBr. 22. And it is likewise irrelevant that CN845 itself had no express "warning against higher levels" when it

[9] Fresenius has not established that the ability to withstand autoclaving has any relationship to the physical stability tests of the Court's construction. *See* TD4 1226:15-1227:20 (Little).

disclosed a limit of 10%. FBr. 22. The relevant prior art simply did not use over 10% emulsifier, had no stability data for formulations over 3%, and would have provided no basis for a POSA to think such high amounts as 14% would work. HBr. § IV.E.2.e; *supra* § II.B.2; TD4 1321:21-1322:6 (Little). Nor would a POSA have imagined Dr. Rabinow's novel and unsupported complexation hypothesis or applied his irrelevant microemulsion art to reach a different conclusion. *See* HBr. §§ IV.E.2.b-c; *supra* §§ II.B.2; TD4 1325:20-1326:1 (Little).

Fresenius fails to consider the most salient facts about the prior art that would inform whether a POSA would have reasonably expected success for the claimed formulation as a whole, including: that aprepitant was known to be very difficult to formulate for intravenous use; that over 20 years of efforts to do so had failed; the hemolytic risk of sodium oleate; and that emulsions, in particular, were one of the more complex formulation strategies in which changing ingredients and amounts could have a cascade of effects. HBr. 44-45.

Fresenius is incorrect that "when answering questions about the reasonable expectation of success, Dr. Little consistently testified only that the claimed emulsifier levels and stability test results had not already been reported in the prior art," and that he "did not contest a POSA's reasonable expectation of success to go above CN845's 10% lecithin level." FBr. 21-22. For example, when asked whether a POSA would have expected 14% to yield a physically stable emulsion, Dr. Little responded that the claimed amounts went "way up higher" than the "industry standard values and what people have shown in the art as being workable." TD4 1321:6-1323:21, 1325:4-1326:1 (Little). Dr. Little likewise opined that a POSA would not have reasonably expected success of the "claimed emulsions" as a whole. TD4 1325:20-1326:1 (Little). It was Fresenius who bore the burden of proof, and Dr. Rabinow who failed to address whether a POSA would have reasonably expected the combination as a whole to succeed. HBr. 44-45.

Finally, it is inappropriate for Fresenius to attempt to use inherency to subvert the reasonable expectation of success requirement. FBr. 36. The proposed combination itself must still meet the requirements for obviousness, including motivation to modify and reasonable expectation of success, which, for all the reasons described above, it does not. *See Honeywell Int'l Inc. v. Mexichem Amanco Holding S.A. DE C.V.*, 865 F.3d 1348, 1355 (Fed. Cir. 2017) ("[T]he Board erred in relying on inherency to dismiss evidence showing unpredictability in the art . . . in order to reject Honeywell's argument that one of ordinary skill would not have been motivated to combine the references with a reasonable expectation of success").

III. OBJECTIVE INDICIA FURTHER DEMONSTRATE NONOBVIOUSNESS

Fresenius argues that Heron has failed to show a nexus "and instead relied upon features 'known in the prior art' including CN845 and Zhou." FBr. 37. Cinvanti®, however, "embodies the claimed features, and is coextensive with them," so "a nexus is presumed and the burden shifts to the party asserting obviousness to present evidence to rebut the presumed nexus." *Alcon Res., Ltd. v. Watson Labs., Inc.*, No. 15-1159-GMS, 2018 WL 1115090, at *25 (D. Del. Mar. 1, 2018). The Asserted Claims do not rely upon features known in the prior art; the claimed formulation is the first and only IV aprepitant formulation for treating CINV, and CN845 and Zhou were not even stable for four days, let alone sufficiently long to commercialize. HBr. § II.C.2.

Fresenius's additional nexus arguments also fail. Fresenius alleges that "none of the Asserted Claims exclude (much less reference) polysorbate 80" (FBr. 51), but such a negative limitation is not required by law. Fresenius also argues that "CN845 and Zhou already taught formulations without using polysorbate 80 [and] Heron did not attempt to distinguish that close prior art" (FBr. 52), but those formulations were not stable and could not be given to patients. *See* HBr. 54-55. Fresenius's assertion that "there is no nexus between the Asserted Claims and the 2-minute push" (FBr. 52-53) is incorrect because the 2-minute IV push is made possible by the

claimed formulation (HBr. 57). And Fresenius's allegation that CN845 "already disclosed both an 'injection' and an 'infusion'" is not only wrong, but also, in any case, far from disclosure of a 2-minute IV push. HBr. 53.

A. Cinvanti® Demonstrated Unexpected Results

Fresenius incorrectly asserts that Heron "failed to compare the Asserted Claims to the closest prior art." FBr. 39. Heron reproduced the CN845 and Zhou formulations in Examples 4 and 5, respectively, and they were confirmed to not be stable, as crystals were observed within four days. HBr. 9-11; 54-55. Fresenius attempts to discount the comparison to Examples 4 and 5 because "they failed to control for pH." FBr. 39. The pH of 7.0 for Example 4 is squarely within the range described in CN845, and the inventors replicated CN845 in Example 4, "pick[ing] components with the best success in terms of making a stable emulsion." HBr. § II.C.2; TD2 490:21-491:5 (Han). Fresenius argues Zhou was not replicated in Example 5 because it did not use the reported pH. FBr. 39. But Dr. Rabinow never made this argument. Instead, Dr. Rabinow agreed "[Example 5] appears to be identical to what was in Zhou." TD2 411:1-5 (Rabinow). Indeed, the parties' experts agreed that Zhou was accurately reproduced. HBr. § II.C.2; *compare* JTX-1.15-16 (18:60-19:26) *with* JTX-115.1; *see also* TD2 410:1-19, 411:7-10 (Rabinow); TD4 1269:4-15, 1402:2-5 (Little). The inventors did not adjust the pH in the Zhou replication because the Zhou paper itself did not adjust pH. TD2 501:1-502:2, 503:9-504:7, 505:17-506:4 (Han).

Moreover, Heron is permitted to rely on evidence, such as test results of Examples 4 and 5, not in the prior art to show that at the time of the invention a POSA would have found the results achieved by the claimed invention unexpected. *See, e.g., Knoll Pharm. v. Teva Pharms. USA*, 367 F.3d 1381, 1385 (Fed. Cir. 2004) ("There is no requirement that an invention's properties and advantages were fully known before the patent application was filed . . . . Nor is it improper to conduct additional experiments and provide later-obtained data in support of patent validity.").

Fresenius is also wrong that "there was nothing 'unexpected' about increasing emulsifier level to increase stability." FBr. 38. This assumption that the prior art was stable is inconsistent with its obviousness assertion that a POSA would have been motivated to increase the emulsifier to the claimed amounts to confer stability. *See supra* § II.B.1. Further, a POSA would not have expected that adding *five times* the level of emulsifier used in the optimized Zhou formulation would result in a stable commercial product. *See supra* § II.C. This distinguishes *BMS* and *Adapt*, where patentee tried to claim properties that a POSA would have expected as unexpected. *See Bristol-Myers Squibb v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 978 (Fed. Cir. 2014) (prior art "already demonstrated 'excellent activity' against the virus"); *Adapt Pharma Ops. Ltd. v. Teva Pharms. USA, Inc.*, 25 F.4th 1354, 1373 (Fed. Cir. 2022) (a POSA would have "expected that using a permeation enhancer such as BZK would result in increased bioavailability").

Fresenius is wrong that "Heron's unexpected results argument relates to a difference in degree and not kind." FBr. 40. The difference between being unstable ***within*** 4 days (prior art) and being stable for at least two months at 25 °C and 10 months at 5 °C, like the patented examples, is a difference in kind because the claimed invention, embodied by Cinvanti®, had, *inter alia*, stability properties that allowed it to be commercialized, unlike the prior art. *See* TD4 1345:24-1346:15, 1347:1-5 (Little); *see also* TD2 541:23-542:7 (Ottobani); *Allergan, Inc. v. Sandoz, Inc.*, 796 F.3d 1293, 1307 (Fed. Cir. 2015) ("difference between an effective and safe drug and one . . . that caused many patients to discontinue treatment" is a "difference in kind"). *Pfizer* is inapposite because the difference there was whether the invention could be "easily manufactured," and in either case, the prior art and the claimed invention could be commercialized. 480 F.3d 1348, 1371 (Fed. Cir. 2007) ("*somewhat* inferior in ease of tableting and projected shelf-life").

B. There Was A Long-Felt But Unmet Need for Cinvanti®

Fresenius argues that Heron failed to show a demonstrated need for a safe and effective IV

NK-1 receptor antagonist with minimal side effects (FBr. 40), but this cannot be reconciled with its argument that a POSA would be seeking to develop such a product. *See* FBr. 6-7, 11. In any case, Heron showed that there was such a need. HBr. 49-51. Fresenius incorrectly asserts that Heron did not identify any particular problem or "efforts to solve any problems with Emend IV." FBr. 41. The Mayo Clinic recognized that the ISAEs with Emend® IV "were a prominent and substantial problem for a significant number of patients," so they switched back to oral aprepitant for certain patients. *See* HBr. 49-50; JTX-137.1-2. The workarounds identified by Fresenius (*e.g.*, central lines, lower concentration/diluted fosaprepitant) serve as direct evidence of efforts to solve the Emend® IV problems, not evidence that "others had previously solved the long-felt need." FBr. 41, 43-45; HBr. 51. Fresenius asserts that, if there was a need, it "was already addressed" by CN845 and Zhou (FBr. 47), however, those formulations had no stability data, could not be given to patients, and were never turned into a commercial product.[10] HBr. 23-24.

In an attempt to dismiss this long-felt need, Fresenius asserts that the "large-scale prospective studies showed Emend IV only caused about 2-3% infusion site issues." FBr. 41. But, these registrational trials for Emend® IV took the best of the best patients who were observed after a single dose, as opposed to what clinicians saw in practice with their patients, including that "these side effects are more prevalent than what was initially reported."[11] TD3 1022:2-1023:14, 1024:8-21 (Roeland); *see also* HBr. 49-50. Fresenius criticizes Dr. Roeland's use of retrospective studies

[10] *In re PepperBall* and *ABT Systems* are inapposite. 469 F. App'x 878, 882 (Fed. Cir. 2012); 797 F.3d 1350 (Fed. Cir. 2015). In *In re PepperBall*, the alleged need had already been met by the prior art, which is not the case here. 469 F. App'x at 883. Similarly, in *ABT Systems*, the claimed benefits of the invention were available in the prior art. 797 F.3d at 1362.

[11] Fresenius asserts that Heron "never established the cause for any potential side effect issue with Emend IV." FBr. 41. This cannot be reconciled with the literature (JTX-137) and the experts' testimony (TD3 1035:6-12, 1050:2-8 (Roeland); TD1 122:16-123:7 (Rabinow)).

(FBr. 42-43), but this is the exact circumstance where retrospective studies can add value, as recognized by Dr. Markman. TD2 727:11-728:15 (Markman). Further, Fresenius's focus on the shared hypersensitivity warning in the product labels ignores the relevant difference between the labels, that Cinvanti®'s label, unlike Emend® IV, does not have an ISAE warning. *Compare* JTX-129 *with* JTX-51; *see also* TD3 1066:5-18 (Roeland).

Fresenius asserts that Dranitsaris shows that the "safety and efficacy of [Cinvanti® and Emend® IV] were 'the same'" (FBr. 45), however, to even be close to Cinvanti®'s safety and efficacy, fosaprepitant (both Emend® IV and generic) required workarounds, and even then, the ISAEs were still numerically higher. JTX-127.1, .4. Dranitsaris actually concluded that to reduce the risk of ISAEs physicians should either use a workaround with a central line (if one is available) or "substitute[e] CINVANTI®" as its formulation does not require such workarounds. JTX-127.9.

Fresenius's assertion that "there was no evidence presented supporting a correlation between polysorbate 80 and [ISAEs]" (FBr. 46) ignores the numerous publications as well as the NCCN Guidelines that demonstrate the industry attributes Emend® IV's ISAEs to polysorbate 80. HBr. 50-51; JTX-139.1; JTX-150.2; JTX-148.2; JTX-155.10; JTX-142.28; *see also* TD3 1035:6-12, 1046:20-1054:20 (Roeland). Further, Fresenius's attempt to recast the "need" to a "need for polysorbate-free formulations" is unfounded. FBr. 47. The need was for an IV NK-1 receptor antagonist that was safe (with minimal side effects) and effective.

C. Others Tried and Failed to Develop a Stable IV Aprepitant Formulation

Despite Fresenius's assertion to the contrary (FBr. 48), Heron provided evidence that those in the art tried, but failed, to develop the claimed invention. HBr. 52-54. Fresenius's assertion that Merck's decision to develop an injectable fosaprepitant formulation is not a failure (FBr. 48-49), discounts the evidence of Merck's failure to develop an intravenous aprepitant product. HBr. 52-53. Indeed, according to Merck, "[t]he sparing water solubility of aprepitant *precluded*

its formulation in a vehicle acceptable for intravenous administration in humans." JTX-82.5; *see also* TD3 914:18-918:10 (Hale). This is why Merck "failed and moved on" in its efforts to develop an IV aprepitant emulsion and had to pivot to fosaprepitant to yield an IV NK-1 receptor antagonist product. *See* TD3 954:3-13, 938:2-21, 942:7-22 (Hale); *see also* PTX-3. Further, Fresenius asserts that whether the formulations of CN845 and Zhou were commercialized is irrelevant (FBr. 48), but these formulations were not shown to be stable, Heron's research showed that they were not stable, and Fresenius points to no further development or clinical trials to show otherwise.

D. Fresenius Copied Cinvanti®

Contrary to Fresenius's assertions (FBr. 50), evidence of copying, has been found to be a respected source of objective evidence of nonobviousness in Hatch-Waxman cases. *See* HBr. 57-58. While Fresenius asserts that "this was not a case where Fresenius Kabi tried to make some other formulation but ultimately resorted to copying Heron's formulation" (FBr. 50), Fresenius, even with its emulsion experience, made the choice to pursue an ANDA and directly copy the formulation instead of pursuing a 505(b)(2) application of the prior art. HBr. 57-58.

E. Cinvanti® Is a Commercial Success

Fresenius does not dispute that Cinvanti® has demonstrated significant sales and market share. HBr. 55-57. Fresenius, however, attempts to shift the focus to cumulative profitability and alleged strategic pricing. FBr. 51-57. Neither can negate Cinvanti®'s commercial success.

Profitability is not required to show commercial success. *See Mitsubishi Tanabe Pharma Corp. v. Sandoz, Inc.*, 533 F. Supp. 3d 170, 209 (D.N.J. 2021) ("[T]he Court does not find that the analysis of profitability factors heavily into the commercial success analysis."). Moreover, Fresenius's analysis relating to profitability looks at only a portion of the life of the Asserted Patents. FBr. 51; TD3 841:15-842:7, 859:12-860:1 (Masztak). Regardless, as Mr. Tate explained, Cinvanti® proved to be profitable on a contribution margin basis. TD4 1147:14-20 (Tate).

There is no dispute pricing matters and can drive sales, however, Fresenius mischaracterizes the impact of pricing on the Cinvanti® sales and market share (FBr. 55), as clinical benefits also factor into the decision. *See, e.g.*, JTX-177.87. Mr. Masztak's focus on 340B pricing, moreover, is irrelevant because 340B hospitals make up about 45% of the Cinvanti® market, meaning 55% of the Cinvanti® market is not eligible for this pricing. TD3 874:23-875:10 (Masztak); JTX-158.90. Fresenius asserts "'in order to compete with Emend IV,' Heron priced Cinvanti® lower than fosaprepitant at launch" (FBr. 55-56), but Cinvanti® was a entering marketplace where Emend® IV was the standard of care, so price needed to be set accordingly. TD4 1159:13-1160:5 (Tate). Moreover, in September 2019, generic fosaprepitant entered the market at a lower price than Cinvanti®, yet Cinvanti® still maintained market share. HBr. 56-57.

Fresenius argues that Heron could not show that being polysorbate 80-free actually resulted in any sales and that "several generic fosaprepitant products containing polysorbate 80 . . . decreased Cinvanti's sales units and net revenues." FBr. 52. But the fact that Cinvanti® costs more and is still being prescribed shows that it is due to the properties of the product, which includes being polysorbate-80 free.[12] TD4 1160:6-1162:8, 1165:11-1166:2 (Tate). That some customers pursue cheaper drugs does not take away from this.

Fresenius's flippant attitude towards time savings for patients and institutions (*e.g.* Dr. Markman's assertion that "2-minute injection push did not provide any real timing benefit in the context of a patient's chemotherapy protocol" (FBr. 53)) cannot be reconciled with the evidence

[12] Fresenius argues that healthcare providers were "generally satisfied with IV Emend safety and indicate low level of concern regarding [injection site reactions] and hypersensitivity" and that "Emend IV adverse events are perceived to be uncommon and not of major concerns." FBr. 52. The first statement reflects predictions made before Cinvanti® was available, and the second statement was a potential barrier viewed by "[s]ome HCPs," and the same cited slide also noted "clinical value proposition (efficacy, safety, formulation)" and the "2 minute IV Push option" as potential drivers for success. JTX-158.32.

in this case, which demonstrates the value to institutions and patients. HBr. 57; JTX-155.[13] Similarly, Fresenius's assertion that "the two-minute IV push cannot be a driver of sales," pointing to a Heron survey (FBr. 53), fails to appreciate that, even if this survey shows that the 30-minute infusion is used, this is still evidence of the flexibility provided by the push. As Mr. Tate explained, "about half of the survey participants used Cinvanti administered in an IV push form, and the other half used the IV infusion." TD4 1174:19-1175:3 (Tate) (discussing JTX-169.59).

IV. FRESENIUS FAILED TO PROVE INVALIDITY UNDER 35 U.S.C. § 112

Fresenius is wrong that the Asserted Claims lack written description support for the pH range of 7.5 to 9.0. Indeed, the range of 7.5 to 9.0 is literally disclosed in the specification:

> In one embodiment, the composition has a pH of about 6 to 9, 7 to 9, 7.5 to 9, 7.5 to 8.5, 8 to 9, 6 to 8, 7 to 8, or 6, 7, 8 or 9.

JTX-1.8 (4:65-67); *see Pharmacyclics LLC v. Alvogen, Inc.*, No. 2021-2270, 2022 WL 16943006, at *11 (Fed. Cir. Nov. 15, 2022) (Bryson, J.) ("The problem for [Defendant], however, is that the precise ranges recited in the claims are found in formulations disclosed in the specification."). Moreover, all of the examples use a pH within that range. JTX-1.14-17 (16:1-18:13, 19:28-21:10).

Fresenius asserts "the specification only shows workable formulations within the narrow pH range of 8.74 to 8.92 (FBr. 57), however, examples are not required for written description. *Allergan*, 796 F.3d at 1308 ("There is no rigid requirement that the disclosure contain 'either examples or an actual reduction to practice'"); *Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1366 (Fed. Cir. 2006) ("[E]xamples are not necessary to support the adequacy of a written description."). Indeed, a POSA would understand from the specification, including the examples,

[13] Fresenius's assertion that the Burns article, from a publication for which Dr. Markman is a peer reviewer, is unreliable because Heron provided funding is hypocritical and unrealistic given the nature of studies in the pharmaceutical area. *See* DTX-131.21; TD3 1024:22-1025:7 (Roeland).

that Heron had possession of formulations with a pH of 7.5-9.0 and proceeded to claim one of the narrowest disclosed ranges (*i.e.*, 1.5 pH units) that covered the examples in the specification.

Fresenius, citing *Purdue Pharma L.P. v. Faulding Inc.*, asserts that "[m]entioning ranges is different than showing possession thereof" (FBr. 58), however, *Purdue Pharma* is not instructive. 230 F.3d 1320 (Fed. Cir. 2000). *Purdue Pharma* found lack of written description because "neither the text accompanying the examples, nor the data, nor anything else in the specification in any way emphasizes the C_{max}/C_{24} ratio." *Id.* at 1326-27. But this is not a case where the limitation claims "a characteristic that is not even discussed even in passing in the disclosure." *See id*. Indeed, as shown above, the specification contains a disclosure coextensive with the exact claimed range. The other cases Fresenius cites are inapposite for the same reason. *See Columbia Ins. Co. v. Simpson Strong-Tie Co. Inc.*, Nos. 2021-2145, 2021-2157, 2023 WL 2733427, at *3 (Fed. Cir. Mar 31, 2023) ("[T]here is nothing in the specification suggesting any sort of upper limit [of the claimed range for a construction product]."); *Biogen Int'l GmbH v. Mylan Pharms.*, 18 F.4th 1333, 1344 (Fed. Cir. 2021) (claims recited "several DMF doses in the 100-1,000 mg/day range as 'effective' without even identifying a target disease").

Fresenius mischaracterizes Dr. Little's testimony in asserting that he "confirmed that the Patents-it-Suit even distinguished away from unclaimed formulations that had been 'adjusted to a pH of less than 8.0'." FBr. 58. This adjustment was done for Example 4, which was a recreation of CN845, and the pH was squarely within the range of CN845. *See* TD4 1413:6-22 (Little). Moreover, in making its obviousness argument, Fresenius asserts that "[a] POSA would have understood that formulations containing aprepitant had been prepared within the pH range of 6.0 to 8.0 expressly disclosed in CN845, and particularly in the basic range at or above 7.0." FBr. 29.[14]

[14] Fresenius misconstrues Dr. Little's testimony showing this pH range worked for Cinvanti® and

V. FRESENIUS'S ANDA PRODUCT INFRINGES THE ASSERTED CLAIMS

Fresenius incorrectly argues that "Dr. Little raised a new claim construction issue regarding the 'physically stable' claim term" because he asserted "that the claimed magnification should refer to an 'objective lens' of 4x to 10x, and coupled with a 'standard' eyepiece of 10x, the magnification should be 40x to 100x." FBr. 59. Far from "rais[ing] a new claim construction issue" (FBr. 59), the Court overruled Fresenius's similar objection to Dr. Little's related testimony at trial and found that he was merely explaining the claim. TD1 22:9-23:2 (Little).[15]

Fresenius is wrong that "[t]o the extent that the 'physically stable' claim term is not an inherent property of the formulation itself, then Heron has not shown infringement" because "Heron did not test Fresenius Kabi's formulation for crystals using any magnification." FBr. 59. As Heron explained, it is not required to specifically test Fresenius's ANDA Product for visible crystals using a microscope with a 10x objective lens in order to demonstrate that none would be visible under this particular test at the claimed conditions. *See* HBr. 16. Heron has demonstrated infringement based on (1) Fresenius's acceptance criteria, (2) Fresenius's (more stringent) testing of its product for crystals, and (3) Heron's visible crystal testing on its own product, to which Fresenius's ANDA Product has an "identical" formulation and is equivalent. HBr. § III.B.

VI. CONCLUSION

For the reasons stated at trial and set forth above and in Heron's opening brief, the Court should issue judgment for Heron on the Asserted Claims.

Fresenius's ANDA Product. FBr. 58. Dr. Little showed that Dr. Rabinow's opinion that the formulations would not work in the lower part of pH range (7.5 to 8.0) is not credible. *See* JTX-33.1 (acceptance criteria pH 7.0-8.6); JTX-47.2 (acceptance criteria pH 7.0 to 9.0).

[15] Fresenius all but admits that 4x to 10x must refer to the objective lens, as the requirement in the Court's construction would otherwise be "trivial." FBr. 35.

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August 15, 2024

CERTIFICATE OF SERVICE

I hereby certify that on August 15, 2024, I caused the foregoing to be electronically filed with the Clerk of the Court using CM/ECF, which will send notification of such filing to all registered participants.

I further certify that I caused copies of the foregoing document to be served on August 15, 2024, upon the following in the manner indicated:

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